REMARKS

Claims 1-3, 6-10, 18, 24-26, 30-34, 44, 46, and 58-64 constitute the pending claims in the present application. Applicants respectfully request reconsideration in view of the following remarks.

In light of conversations with Examiner James Wilson, Applicants submit that the remarks already of record adequately address the rejections under 35 U.S.C. § 112 raised in the Office Action. Applicants again point out that identical language was allowed without objection in two related cases. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-3, 7, 24-26, 32-33, 58-60, and 62-64 are rejected under 35 U.S.C. §102(b) as being anticipated by EP 502194. Applicants respectfully traverse this rejection.

Applicants submit that for the reasons already of record, this rejection is untenable. The new argument put forth by the Examiner presents no new issues. All of the pending claims recite that the polymer is water-soluble. Accordingly, any allegedly anticipatory material must have this characteristic, either explicitly or inherently. The Examiner apparently relies on "low-molecular weight oligomers" that were "extracted with hot ethanol" as anticipating the presently claimed invention, including the characteristic of being water-soluble. Not only does this description alone fail to demonstrate water-solubility, but the context makes it clear that the low-molecular weight oligomers are *not* water-soluble. In the sentence preceding the sentence relied on by the Examiner, "the precipitate is washed with methanol." As explained in Applicants' prior response, methanol is more polar than ethanol, and thus closer in solubilization properties to water than is ethanol. For this reason, any water-soluble material that would dissolve in hot ethanol would be expected to dissolve in the methanol as well. Yet this is clearly not true of the low-molecular weight oligomers in question. Since this appears to be the only material that the Examiner alleges to be water-soluble, Applicants submit that the current rejection lacks factual basis and must be withdrawn. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-3, 7, 24-26, 32-33, 58-60, and 62-64 are rejected under 35 U.S.C. §102(b) as being anticipated by Ceccato et al. Applicants respectfully traverse this rejection.

Ceccato et al. disclose a molecular tube formed from axially aligned cyclodextrin units that have been linked together using epichlorohydrin. As can be seen from the schematic diagram in Figure 2, the successive cyclodextrin units are joined by multiple connections, due to the unselective nature of the epichlorohydrin reaction. In contrast, claim 1 is directed to a linear cyclodextrin polymer comprising cyclodextrin units that, as depicted schematically, have exactly two linkages whereby the polymer chain is extended, thereby resulting in a linear polymer chain. The molecular tube disclosed by Ceccato et al. lacks such units. Indeed, if the tube disclosed by Ceccato *did* have such units, the cyclodetrin units would not be locked into their coaxial arrangement and the tube-like qualities would be irrevocably lost as soon as the axial PEG chain is removed. Accordingly, the molecular tubes taught by Ceccato et al. do not meet all the limitations of claim 1.

There is no teaching in Ceccato et al. that appears even to approximate the methods of claims 24-26 or the method set forth in claim 58, and it is not apparent why these claims are subject to rejection over this reference. The methods of preparation taught by Ceccato et al. appear to be entirely different, having few if any features in common with the methods defined in these claims. Clarification is respectfully requested.

Claims 59, 60, and 62-63 have been amended to state that each cyclodextrin moiety is attached to up to two linker moieties. Claim 64 already included a limitation that the cyclodextrin moieties are attached to at most two occurrences of the linker A. As described above, the cyclodextrin moieties in the tube disclosed by Ceccato et al. not only are depicted as being attached to four or five linker moieties each, but must necessarily be linked in this way if the integrity of the tube is to be maintained. Accordingly, Applicants submit that these claims as amended are not anticipated by Ceccato et al. Reconsideration and withdrawal of this rejection are respectfully requested.

As the remaining claims subject to this rejection depend from the independent claims considered above, Applicants submit that none of the pending claims are anticipated by Ceccato et al. and the rejection should be withdrawn.

Claims 1-3, 7, 24-26, 32-33, 58-60, and 62-64 are rejected under 35 U.S.C. §102(b) as being anticipated by Harada et al. Applicants respectfully traverse this rejection.

Harada et al., like Ceccato et al., disclose a tubular polymer formed from cyclodextrins linked by epichlorohydrin. Also like Ceccato et al., the successive cyclodextrin units are joined by multiple connections, due to the unselective nature of the epichlorohydrin reaction, as can be seen from the schematic diagram in Figure 1 of Harada et al. Similarly, the multiple connections are required to stabilize the carefully-assembled tubular structure. As a result, Harada et al. does not anticipate the pending claims for the exact reasons discussed above with reference to Ceccato et al. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-3, 7, 24-26, 32-33, 58-60, and 62-64 are rejected under 35 U.S.C. §102(b) as being anticipated by two references by Uekama et al. Applicants respectfully traverse this rejection. As Applicants can discern no differences between these references that would impact the arguments below, Applicants will address these references together.

Uekama et al. disclose experiments using polymers of cyclodextrin and epichlorohydrin. The Examiner points to Table I of one of the references, which implies that dimers and trimers of cyclodextrin make up a substantial portion of the material tested. The Examiner asserts that these must be linear polymers.

Applicants attach herewith a copy of the Hoffman reference cited by Uekama as disclosing the procedure for preparing the cyclodextrin materials. On page 1149 of this reference, 50 g of cycloheptaamylose (β-cyclodextrin) is taught for reaction with 34 mL epichlorohydrin. At a molecular weight of 1135, this translates to 44 mmol of

cyclodextrin. The epichlorohydrin, at a density of 1.18 g/mL and a molecular weight of only 92.5, amounts to 433 mmol, almost ten times as much as the cyclodextrin.

Applicants point out, as has already been made of record, that epichlorohydrin is a highly reactive and non-selective coupling reagent under the disclosed polymerization conditions. Each cyclodextrin molecule presents multiple reactive hydroxyls that are reactive with epichlorohydrin. Because entropy favors intramolecular interactions, since the reactive elements are held in close proximity to each other, cyclodextrin molecules, once linked intermolecularly, are highly likely to undergo further *intramolecular* coupling. Thus, a putative dimer formed under these conditions is likely to have multiple linkages between the two cyclodextrin moieties. A putative trimer may also have such extra linkages, and can even cyclize intramolecularly to form a ring (or triangle) of three cyclodextrin moieties. With ten equivalents of epichlorohydrin for each cyclodextrin, such multiple linkages will not be the exception, but the rule.

As stated above, claim 1 is directed to a linear cyclodextrin polymer comprising cyclodextrin units that, as depicted schematically, have exactly two linkages whereby the polymer chain is extended, thereby resulting in a linear polymer chain. Such units will be formed only rarely, if at all, under the Hoffman/Uekama conditions.

As already made of record, even if some few simple dimers or trimers with at most two linkers per cyclodextrin were present in the Uekama/Hoffman material as impurities, that fact would be insufficient to anticipate the presently claimed invention. The Supreme Court held, in *Tilghman v. Proctor*, 102 U.S. 707, 711, (1881) that "If the [claimed invention] were accidentally and unwittingly produced, whilst the operators were in pursuit of other and different results, without exciting attention and without its even being known what was done or how it had been done, it would be absurd to say that this was an anticipation of Tilghman's discovery." Similarly, *International Nickel Co. v. Ford Motor Co.*, 166 F.Supp. 551, 560-61, (S.D.N.Y. 1958) held that "[w]here the allegedly anticipating product was produced merely by chance and never recognized or appreciated, one who later discovers and recognizes the product may patent it." The present situation falls squarely within this analysis. If indeed any dimers or trimers with

at most two linkers per cyclodextrin were present in the Uekama/Hoffman composition, they were created solely by chance, rather than by design. The reference shows absolutely no recognition or appreciation of any dimers or trimers with at most two linkers per cyclodextrin that may have been present. Accordingly, to hold the present claims anticipated by Uekama et al. flies in the face of established Supreme Court precedent.

Particularly appropriate to the present situation, *Pfizer, Inc. v. International Rectifier Corp.*, 545 F. Supp. 486, 508, 207 USPQ 397 (C.D. Calif. 1980), *aff'd*, 635 F.2d 357, 217 USPQ 39 (9th Cir. 1982), *cert. denied*, 459 U.S. 1172 (1983) stands for the proposition that "it has never been the law that unrecognized or unappreciated coproduction of a small amount of a compound without a suggestion of that fact being shown in the prior art can be held as anticipating that compound." See also *In re Coordinated Pretrial Proceedings in Antibiotic Actions*, 498 F. Supp. 28, 35 (E.D. Pa. 1980). Thus, it is insufficient as a matter of law for the Examiner to assert that the present claims are anticipated because of some remote possibility that dimers or trimers with at most two linkers per cyclodextrin might have been present as an impurity in the Uekama/Hoffman composition.

With respect to the methods of claims 24-26 or the method set forth in claim 58, there is no teaching in Uekama et al. that appears even to approximate these methods, and it is not apparent why these claims are subject to rejection over this reference. The methods of preparation taught by Uekama et al. appear to be entirely different, having no resemblance to the methods defined in these claims. Clarification is respectfully requested.

Claims 59, 60, and 62-63 have been amended to state that each cyclodextrin moiety is attached to up to two linker moieties. Claim 64 already included a limitation that the cyclodextrin moieties are attached to at most two occurrences of the linker A. As described above, the cyclodextrin moieties in the Uekama/Hoffman material would be predominantly if not exclusively connected through multiple linkages. Accordingly,

Applicants submit that these claims as amended are not anticipated by Uekama et al. Reconsideration and withdrawal of this rejection are respectfully requested.

Claims 1-3, 7, 24-26, 32-33, 58-60, and 62-64 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Harada et al. in view of Ceccato et al., both of which were addressed separately above. Applicants respectfully traverse this rejection.

Pursuant to MPEP 706.02(j), three basic criteria have to be met before a *prima facie* case of obviousness rejection can be made: 1) the prior art references must teach or suggest all the claim limitations; 2) some motivation or suggestion, either found in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine or modify the references must be present; and 3) a reasonable expectation of success is required.

As noted above, Harada et al. and Ceccato et al., which are highly similar to each other, fail to anticipate the pending claims for exactly the same reasons. As pointed out above, neither reference teaches polymers wherein the non-terminal cyclodextrin moieties have up to two linkages to other cyclodextrin moieties. Rather, both references disclose polymers where adjacent cyclodextrin moieties are coupled by multiple linkages. These multiple linkages are required to achieve and maintain the tubular structure sought by the researchers; otherwise, the carefully assembled structures would fall apart as soon as the axial PEG molecule was removed. Accordingly, the references, taken together, fail to teach all the claim limitations. They also fail to provide a suggestion to arrive at the claimed linear polymers, which would necessarily lack the tubular structure the authors went to great lengths to achieve. Accordingly, this combination of references fails to render the presently claimed subject matter obvious. Reconsideration and withdrawal of this rejection are respectfully requested.

CONCLUSION

For the foregoing reasons, Applicants respectfully request reconsideration and withdrawal of the pending rejections. Applicants believe that the claims are now in condition for allowance and early notification to this effect is earnestly solicited. As suggested by Examiner Wilson in a telephonic interview, **Applicants respectfully**

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request that all future communications from the Office in this case be reviewed by a supervisor prior to being mailed. Furthermore, **Applicants respectfully request an interview with the Examiner and his supervisor before the mailing of any further rejection of claims in this application**. Any questions arising from this submission may be directed to the undersigned at (617) 951-7000.

Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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David P. Halstead, Ph.D.
Reg. No. 44,735

Customer No: 28120
Docketing Specialist
Ropes & Gray LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050